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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification:</b> A61K 31/37, 31/70, 31/44, 31/27, 31/12, 31/13, 31/415		<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 99/27919</b>
			<b>(43) International Publication Date:</b> 10 June 1999 (10.06.99)
<b>(21) International Application Number:</b> PCT/CA98/01093		<b>(74) Agent:</b> BERESKIN & PARR; 40th floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).	
<b>(22) International Filing Date:</b> 1 December 1998 (01.12.98)			
<b>(30) Priority Data:</b> 60/067,020 1 December 1997 (01.12.97) US 60/067,021 1 December 1997 (01.12.97) US 60/084,847 8 May 1998 (08.05.98) US 60/107,392 6 November 1998 (06.11.98) US		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
<b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b> US PCT/CA97/00506 (CIP) Filed on 17 July 1997 (17.07.97)		<b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(71) Applicant (for all designated States except US):</b> NICOGEN INC. [CA/CA]; Suite 1506, 150 York Street, Toronto, Ontario M5H 3S5 (CA).		<b>(88) Date of publication of the international search report:</b> 12 August 1999 (12.08.99)	
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SELLERS, Edward, M. [CA/CA]; 78 Baby Point Crescent, Toronto, Ontario M6S 1B2 (CA). TYNDALE, Rachel, F. [CA/CA]; 28 Brunswick Avenue #5, Toronto, Ontario M5S 2L7 (CA).			
<b>(54) Title:</b> CYP2A ENZYMES AND THEIR USE IN THERAPEUTIC AND DIAGNOSTIC METHODS			
<b>(57) Abstract</b> <p>A method of regulating the activity of human cytochrome P450 isozyme CYP2A6 to control nicotine metabolism or decrease the production of carcinogens from procarcinogens, such as those present in tobacco smoke, in an individual by selectively inhibiting CYP2A6. Various prophylactic (i.e., prevention and treatment) compositions and methods are also described, including an improved oral nicotine composition and method comprising the use of nicotine together with an inhibitor of the CYP2A6 enzyme. Furthermore, it has been discovered that the presence in an individual of a mutant allele of human cytochrome P450 enzyme CYP2A6 (referred to throughout this specification as "CYP2A6" for brevity) is predictive of an individual who: (i) has a decreased risk of becoming a smoker, (ii) will smoke less if he/she becomes dependent, and/or (iii) may be at relatively lower risk for cancer due to both decreased smoke exposure and decreased CYP2A6-mediated activation of tobacco smoke and other procarcinogenic substrates. This invention provides diagnostic methods for predicting tobacco dependence risk and risk for cancers related to CYP2A6 substrates in an individual by analysing for the presence of a mutant genotype for human cytochrome P450 enzyme CYP2A6 in an individual, ranging from gene duplication (multiple copies of CYP2A6) to single or even no copies due to null alleles or gene deletion.</p>			

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/01093

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/37 A61K31/70 A61K31/44 A61K31/27 A61K31/12  
A61K31/13 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. NAKAJIMA ET AL.: "Characterization of CYP2A6 involved in 3'-hydroxylation of cotinine in human liver microsomes." J. PHARMACOL. EXP. THERAP., vol. 277, no. 2, 1996, pages 1010-1015, XP002050001 see the whole document	1-4,7-9, 11-13, 16,34-36
P,X	M. NAKAJIMA ET AL.: "Role of human cytochrome P4502A6 in C-oxidation of nicotine." DRUG METABOL. DISPOS., vol. 24, no. 11, 1996, pages 1212-1217, XP002050002 see the whole document	1-4,7-9, 11-13, 16,34-36
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

11 June 1999

Date of mailing of the international search report

21/06/1999

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/01093

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	A. TSUJIMOTO ET AL.: "Potent inhibitory action of pilocarpine on hepatic drug metabolism." JPN. J. PHARMACOL., vol. 22, no. 5, 1972, pages 736-739, XP002050003 see the whole document	1-4,7-9, 11-13, 16,34-36
X	A. TSUJIMOTO ET AL.: "A study of the nature of pilocarpine inhibition of hepatic drug-metabolizing enzymes." BIOCHEM. PHARMACOL., vol. 26, no. 21, 1977, pages 2072-2074, XP002050004 see the whole document	1-4,7-9, 11-13, 16,34-36
A	H. FOTH ET AL.: "Nicotine metabolism in isolated perfused lung and liver of phenobarbital- and benzoflavone-treated rats." ARCH. TOXICOL., vol. 65, no. 1, 1991, pages 68-72, XP002050005	
A	G.A. KYEREMATEN ET AL.: "Metabolism of nicotine by hepatocytes." BIOCHEM. PHARMACOL., vol. 40, no. 8, 1990, pages 1747-1756, XP002050006	
A	H. YAMAZAKI ET AL.: "Cytochrome P450 sE1 and 2A6 enzymes as major catalysts for metabolic activation of N-nitrosodialkylamines and tobacco-related nitrosamines in human liver microsomes." CARCINOGENESIS, vol. 13, no. 10, 1992, pages 1789-1794, XP002050007	
A	WO 95 34679 A (USA DEPARTMENT OF HEALTH AND HUMAN SERVICES) 21 December 1995	

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 98/ 01093

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —  
because they relate to subject matter not required to be searched by this Authority, namely:  
See FURTHER INFORMATION SHEET PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claim(s) 25 to 29, 31 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.  
Although claims 1 to 15, 22, 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 98/01093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9534679 A	21-12-1995	AU 2860295 A	05-01-1996
		GB 2303853 A,B	05-03-1997
		US 5891633 A	06-04-1999

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